URUKUNDO, ICYIZERE N'UBUVUZI

Preparing People Living with Schizophrenia for a Better Future

A guide to preparing people living with schizophrenia for long-term treatment

Republic of Rwanda
Ministry of Health

rbc Rwanda Biomedical Centre

Johnson & Johnson

Introduction

Schizophrenia is serious and lifelong mental illness, but with timely diagnosis and evaluation, with the right treatment, and with the skills and dedication of close family members and a multi-disciplinary team, symptoms can improve and patients can go on to live productive lives.

This series of booklets has been developed to outline the many different aspects of schizophrenia and its treatment. Their aim is to act as an accessible resource to help the HCPs, caregivers and family of people living with schizophrenia provide the best support possible.

This is the fourth in a series of booklets and matching videos available to all health care providers working in mental health in Rwanda. In this booklet, and in the accompanying video of the same name, we will explore ways we can better prepare people living with schizophrenia for long-term treatment, promote compliance and help them avoid relapse.

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Treatment Aims

The overarching aims of treatment planning must be to:

- promote and maintain recovery
- maximize quality of life and adaptive functioning
- reduce or eliminate symptoms

To achieve these aims, it is crucial to identify the patient's aspirations, goals for treatment, and treatment-related preferences.

One of the widely-used treatment guidelines for schizophrenia are those by the American Psychiatric Association (APA). This brochure uses information from the latest version of the guidelines, which is available at: The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia.[1] These guidelines recommend that people with schizophrenia have a documented, comprehensive, and person-centered treatment plan that includes evidence-based non-pharmacological and pharmacological treatments.

The optimal treatment of schizophrenia will, of course, depend on the individual, their social circumstances, risk factors, comorbidities and treatment history.

Because treatment is a lifelong process, it will inevitably need adjusting as time goes on.

Engaging Family Members & Other Support People

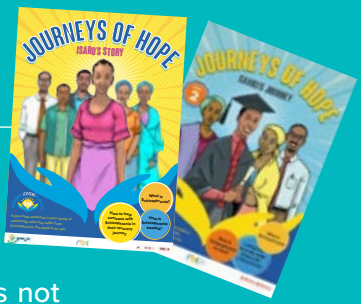
Identifying and monitoring all of the factors involved in the development of a treatment plan is a complex process, and it is often helpful to consult with both the patient and their caregivers and family – not only at initial assessment, but as treatment proceeds and the treatment plan is updated.

Family members and others involved in the patient's life may express specific concerns about the individual's symptoms or behaviours, which, if present, should be documented and addressed.

For many people in Rwanda, praying and attending church are an integral component in healing and recovery, and this must be acknowledged and affirmed. But always emphasize that medicine is the cornerstone of treatment for schizophrenia and taking one's medication regularly is the most important action for recovery. Remind patients that they can take medicine and also pray.

Most patients welcome the involvement of family members and caregivers. As the healthcare provider, you should champion and encourage this involvement as it can have a transformative impact on a patient's journey.

You can actively engage caregivers and family members by explaining to them how they can play an important role on the care team, providing educational materials, and directing them to relevant organizations for support.



A common barrier to good collaboration between patients and healthcare providers is the real – or perceived – stigma that a patient does not have the mental capacity to provide reliable information, opinions or insight into his or her treatment.

You can break down this barrier by inviting the patient to speak openly and listening to his or her opinions on their treatment course. Encourage patients to keep treatment diaries, like the ones found in the illustrated comics that are part of our "Love Hope and Treatment" campaign. Make sure they feel confident that you will listen to their opinions and insights.

Monitoring

RISK FACTORS

There are multiple risk factors to be monitored with people living with schizophrenia. Here we will just highlight some of the most common ones around suicide, aggression and overall mortality.

Identifying risk factors for suicidal and aggressive behaviours is an important part of developing a treatment plan.

The treatment plan should prepare for those periods where there is an increased risk of suicidal and aggressive behaviours, such as just after diagnosis or subsequent to hospital discharge.

Cannabis use may augment symptom severity in patients with schizophrenia, and other substance use disorders are

associated with a poorer prognosis in these individuals, increasing the risk of suicide or aggressive behaviour. Thus, it is important for the treatment plan to address substance use disorders when they are present.

Smoking is a risk factor for increased mortality in individuals with serious mental illness. Smoking cessation approaches will typically follow guidelines for the general population, but it should be noted that smoking cessation may be lower in individuals with schizophrenia than in the general population.

DURING TREATMENT

During treatment with an antipsychotic medication, it is important to monitor:

- medication adherence
- therapeutic benefits
- treatment-related side effects

If a lack of response is noted, additional assessment will be needed to identify and address possible contributors, including nonadherence. Regular monitoring can help detect a return of symptoms prior to a more serious relapse.

Monitoring for the presence of side effects is also important throughout the course of antipsychotic treatment. Some side effects may dissipate after treatment initiation, whilst others may emerge or increase in severity as treatment continues.

While the side effects may occur, but in most cases, they are manageable. The next section outlines the potential adverse effects experienced with antipsychotic treatments, followed by a guide to general strategies for their management.

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Potential Adverse Effects Experienced with Antipsychotics and Management Strategy

ALLERGIC AND DERMATOLOGICAL EFFECTS

Cutaneous allergic reactions occur infrequently with antipsychotic medications, but hypersensitivity can manifest as maculopapular erythematous rashes typically of the trunk, face, neck, and extremities. Medication discontinuation or administration of an antihistamine is usually effective in reversing these symptoms.

CARDIOVASCULAR EFFECTS

Hyperlipidemia

Certain antipsychotic medications may increase the risk of hyperlipidemia. In any patient with hyperlipidemia, it is also important to assess for other contributors to metabolic syndrome and ensure that the patient is receiving treatment with a lipid-lowering agent, as clinically indicated.

Myocarditis and cardiomyopathy

Myocarditis and cardiomyopathy have been reported in some patients treated with clozapine and have resulted in death in some individuals. For myocarditis, the reported incidence has varied from 0.015% to 8.5%. For cardiomyopathy, the reported incidence appears to be considerably lower than rates of clozapine-associated myocarditis.

Although cardiomyopathy has been reported throughout the course of clozapine treatment, the onset of myocarditis is typically during the first month of treatment and heralded by shortness of breath, tachycardia, and fever. Other features can include fatigue, chest pain, palpitations, and peripheral edema. Diagnosis can be challenging due to the non-specific nature of these symptoms.

In patients who do develop myocarditis or cardiomyopathy in conjunction with clozapine treatment, clozapine is typically discontinued. Subsequent decisions about resuming clozapine are individualized and based on the benefits and risks of treatment as compared to other therapeutic alternatives.

Orthostatic hypotension
Orthostatic hypotension (a drop-in blood pressure when changing from lying or sitting to standing) is dose-related and due to the alpha-receptor blocking effects of antipsychotic medications.

When severe, orthostatic hypotension can cause syncope, dizziness, or falls. Older or severely debilitated patients, patients in the dose-titration phase of clozapine therapy, and patients with peripheral vascular disease or a compromised cardiovascular status may be at particular risk.

Patients who experience orthostatic hypotension must be cautioned to sit on the edge of the bed for a minute before standing up, to move slowly when going from lying or sitting to standing and to seek assistance when needed.

Management strategies for orthostatic hypotension include using supportive measures (e.g., use of support stockings, increased dietary salt and fluid intake), reducing the speed of antipsychotic dose titration, decreasing or dividing doses of antipsychotic medication, switching to an antipsychotic medication without antiadrenergic effects, and, as a last resort, administering the salt/fluid retaining corticosteroid, fludrocortisone, to increase intravascular volume.

For patients who are receiving concomitant antihypertensive treatment, adjustments to the dose of these medications may be needed.

QTc Prolongation
When the QTc interval is prolonged, a decision about antipsychotic medication choice or changes requires a comprehensive risk-benefit assessment. A QTc interval > 500 msec is sometimes viewed as a threshold for concern; however, there is no absolute QTc interval at which a psychotropic should not be used.

Factors to consider when making a determination about selecting or changing antipsychotic medications include whether the patient is taking other medications that are known to prolong QTc intervals; whether the patient has factors that would influence drug metabolism leading to higher blood levels of a drug (e.g., poor metabolizer status, pharmacokinetic drug-drug interactions, hepatic or renal disease, drug toxicity); whether the patient is known to have a significant cardiac risk factor (e.g., congenital long QT syndrome, structural or functional cardiac disease, bradycardia, family history of sudden cardiac death); or other factors associated with an increased risk of TdP (e.g., female sex, advanced age, personal history of drug-induced QTc prolongation, severe acute illness, starvation, or risk or presence of hypokalemia, hypomagnesemia, or hypocalcemia). For individuals with these risk factors, antipsychotic medications with regulatory warning or those with a known risk of QTc prolongation are not recommended for use if safer medication alternatives are available.

Tachycardia

Tachycardia appears to be particularly common in individuals who are treated with clozapine, but may also be seen in individuals treated with other antipsychotic medications, particularly low-potency phenothiazines.

Although healthy patients may be able to tolerate some increase in resting pulse rate, this may not be the case for patients with pre-existing heart disease.

In patients with significant tachycardia (heart rates above 110 to 120 bpm), an ECG is warranted as is an assessment for other potential causes of tachycardia (e.g., fever, anemia, smoking, hyperthyroidism, respiratory disease, cardiovascular disorders, caffeine and other stimulants, and side effects of other medications).

Management strategies for tachycardia with antipsychotic medications include reducing the dose of medication, discontinuing medications with anticholinergic or stimulant properties, and using the strategies described above to reduce any contributing orthostatic hypotension.

If tachycardia is accompanied by pain, shortness of breath, fever, or signs of a myocardial infarction or heart rhythm problem, emergency assessment is essential.

ENDOCRINE SIDE EFFECTS

Glucose dysregulation and diabetes mellitus

Evidence from clinical trials suggests that some antipsychotic medications are associated with an increased risk of hyperglycemia and diabetes. Complicating the evaluation of antipsychotic-related risk of diabetes is that some patients with first-episode psychosis seem to have abnormal glucose regulation that precedes antipsychotic treatment. In addition, obesity and treatment-related weight gain may contribute to diabetes risk.

Nevertheless, there are some patients without other known risk factors who develop insulin resistance early in the course of antipsychotic treatment. When individuals with schizophrenia do develop diabetes, management principles should follow current guidelines for any patient with diabetes. The clinician can also help in ensuring that patients are obtaining appropriate diabetes care, given frequent health disparities for individuals with serious mental illness, and encourage patients to engage in lifestyle interventions to improve diabetes self-management.

Hyperprolactinemia

Prolactin elevation is frequent in patients treated with antipsychotics, which increase prolactin secretion by blocking the inhibitory actions of dopamine on lactotrophic cells in the anterior pituitary. Consequently, hyperprolactinemia is observed more frequently with the use of antipsychotics that are more potent at blocking dopamine receptors.

In both men and women, prolactin-related disruption of the hypothalamic-pituitary-gonadal axis can lead to decreased sexual interest and impaired sexual function. Other effects of hyperprolactinemia may include breast tenderness, breast enlargement, and lactation. Because prolactin also regulates gonadal function, hyperprolactinemia can lead to decreased production of gonadal hormones, including estrogen and testosterone, resulting in disruption or elimination of menstrual cycles in women. In addition, in lactating mothers, suppression of prolactin may be detrimental, and the potential for this effect should be considered.

If a patient is experiencing clinical symptoms of prolactin elevation, the dose of antipsychotic may be reduced or the medication regimen may be switched to an antipsychotic with less effect on prolactin such as an antipsychotic with partial agonist activity at dopamine receptors. Administering of a dopamine agonist such as bromocriptine may also be considered.

Sexual Function Disturbances

A majority of patients with schizophrenia report some difficulties with sexual function. Although multiple factors are likely to contribute and rates vary widely depending on the study, it is clear that antipsychotic treatment contributes to sexual dysfunction.

Effects of antipsychotic agents on sexual function may be mediated directly via drug actions on adrenergic and serotonergic receptors or indirectly through effects on prolactin and gonadal hormones. Loss of libido and anorgasmia can occur in men and in women; erectile dysfunction and ejaculatory disturbances also occur in men. Retrograde ejaculation has also been reported with specific antipsychotic medications. In addition, it is important to note that priapism can also occur in association with antipsychotic treatment, particularly in individuals with other underlying risk factors such as sickle cell disease.

Despite the high rates of occurrence of sexual dysfunction with antipsychotic medication, many patients will not spontaneously report such difficulties. Thus, it is important to ask patients specifically about these side effects. Education about sexual side effects of medication can also be provided to the patient to communicate that these symptoms may occur but can be addressed.

When sexual side effects of antipsychotic therapy are of significant concern to the patient, a reduction in medication dose or change in medication may be considered in addition to an assessment of other potential contributing factors (e.g., hyperprolactinemia, other medications, psychosocial factors). Priapism, if it occurs, requires urgent urological consultation.

GASTROINTESTINAL SIDE EFFECTS

The most common gastrointestinal side effects of antipsychotic medications are related to anticholinergic side effects and include dry mouth and constipation. Patients and families should be educated about monitoring for constipation and, if present, constipation should be reported promptly to clinicians.

To prevent development of constipation, it is useful to minimize the doses and number of contributory medications such as other anticholinergic medications and opioids. Activity and exercise should be encouraged to stimulate motility.

If constipation does develop, initial treatment can include stool softeners or osmotic laxatives. Second line treatments include stimulant laxatives. If constipation persists, an enema should be considered. A combination of treatments may be needed to treat constipation and then to prevent its recurrence.

HEMATOLOGICAL EFFECTS

Hematological effects are of greatest concern with clozapine; however, they have also been reported with other antipsychotic agents and may include inhibition of leukopoiesis, purpura, hemolytic anemia, and pancytopenia. There is no clear etiology of severe neutropenia or agranulocytosis, when most extreme. If severe neutropenia does develop, it is usually reversible if clozapine is discontinued immediately and secondary complications (e.g., sepsis) are given intensive treatment.

NEUROLOGICAL SIDE EFFECTS

Acute dystonia

Medication-induced acute dystonia is defined by the DSM-5 as the “abnormal and prolonged contraction of the muscles of the eyes (oculogyric crisis), head, neck (torticollis or retrocollis), limbs, or trunk developing within a few days of starting or raising the dosage of a medication (such as a neuroleptic) or after reducing the dosage of a medication used to treat extrapyramidal symptoms” (American Psychiatric Association 2013).

Acute dystonia is sudden in onset and painful and can cause patients great distress. Because of its dramatic appearance, health professionals who are unfamiliar with acute dystonia may incorrectly attribute these reactions to catatonic signs or unusual re-exist on the part of patients, whereas oculogyric crises can sometimes be misinterpreted as indicative of seizure activity.

In individuals treated with FGAs (First Genertation Antipsychotics), it is estimated that up to 10% may experience an acute dystonic episode and, with SGAs (Second Genertation Antipsychotics), rates of acute dystonia may be less than 2%. Additional factors that increase the risk of acute dystonia with antipsychotic medication include young age, male gender, ethnicity, recent cocaine use, high medication dose, and intramuscular route of medication administration.

Akathisia

Medication-induced acute akathisia is defined by the DSM-5 as "subjective complaints of restlessness, often accompanied by observed excessive movements (e.g., fidgety movements of the legs, rocking from foot to foot, pacing, inability to sit or stand still), developing within a few weeks of starting or raising the dosage of a medication (such as a neuroleptic) or after reducing the dosage of a medication used to treat extrapyramidal symptoms" (American Psychiatric Association 2013).

Akathisia is sometimes difficult to distinguish from psychomotor agitation associated with psychosis, leading to a cycle of increasing doses of antipsychotic medication that lead to further increases in akathisia. Even in mild forms in which the patient is able to control most movements, akathisia is often extremely distressing to patients, is a frequent cause of nonadherence with antipsychotic treatment, and, if allowed to persist, can contribute to feelings of dysphoria and, in some instances, suicidal behaviors.

The reported rates of akathisia vary from 10%-15% to as many as one-third of patients treated with antipsychotic medication, even when SGAs are used.

Parkinsonism

Medication-induced parkinsonism, which is termed neuroleptic-induced parkinsonism in DSM-5, is defined as "parkinsonian tremor, muscular rigidity, akinesia (i.e., loss of movement or difficulty initiating movement), or bradykinesia (i.e., slowing movement) developing within a few weeks of starting or raising the dosage of a medication (e.g., a neuroleptic) or after reducing the dosage of a medication used to treat extrapyramidal symptoms" (American Psychiatric Association 2013).

These symptoms of medication-induced parkinsonism are dose dependent and generally resolve with discontinuation of antipsychotic medication. It is important to appreciate that medication-induced parkinsonism can affect emotional and cognitive function, at times in the absence of detectable motor symptoms. As a result, it can be difficult to distinguish the negative symptoms of schizophrenia or concomitant depression from medication-induced parkinsonism. In addition, emotional and cognitive features of medication-induced parkinsonism can be subjectively unpleasant and can contribute to poor medication adherence.

Neuroleptic Malignant Syndrome (NMS)

NMS is characterized by a classic triad of rigidity, hyperthermia, and sympathetic nervous system lability, including hypertension and tachycardia, in the context of

exposure to a dopamine antagonist (or withdrawal of a dopamine agonist), typically within 72 hours of symptom development.

In addition, NMS is associated with an elevated level of serum creatine kinase (typically, at least four times the upper limit of normal), tachypnea, change in mental status (e.g., delirium, stupor), and lack of another identified etiology for the symptoms. Notably, however, the onset and clinical features of NMS can vary and may make recognition more difficult. If misdiagnosed and if mistreated, NMS can be fatal.

Other diagnostic considerations in patients presenting with possible NMS include malignant catatonia, malignant hyperthermia (in association with anesthetic administration), heat stroke (for which patients treated with antipsychotics have a heightened susceptibility), serotonin syndrome (in patients also taking serotonergic drugs such as selective serotonin reuptake inhibitors), “benign” elevations in the level of serum creatine kinase, fever in association with clozapine treatment, alcohol or sedative withdrawal, anticholinergic syndrome, hyperthermia associated with use of stimulants and hallucinogens, central nervous system infections, limbic encephalitis, and inflammatory or autoimmune conditions.

NMS has been reported with almost all medications that block dopamine receptors, but high-potency FGAs appear to be associated with a greater risk of occurrence. Risk also may be increased by use of short-acting intramuscular formulations of antipsychotic medications, use of higher total drug dosages, or rapid increases in the dosage of the antipsychotic medication. Additional risk factors for NMS include acute agitation, dehydration, exhaustion, iron deficiency, physical illness, re-existing neurological disability, and a prior episode of NMS.

NMS is rare, with an estimated incidence of 0.01%-0.02% among individuals treated with antipsychotics. However, antipsychotic medications should always be discontinued, and supportive treatment to maintain hydration and to treat the fever and cardiovascular, renal, or other symptoms should be provided. NMS is usually self-limited with resolution within a week of medication discontinuation in the majority of patients; however, prolonged symptoms of NMS do occur and may be associated with use of LAI (Long-Acting Injectables) antipsychotic medications.

Seizures

Among the antipsychotic medications, clozapine is associated with the greatest likelihood of a seizure and patients with a history of an idiopathic or medication-induced seizure may have a higher risk. Although generalized tonic-clonic seizures are most frequent, other types of seizures may occur. Seizures may also be preceded by myoclonus or drop attacks.

FGAs can also lower the seizure threshold in a dose-related manner and result in the development of generalized tonic-clonic seizures. Nevertheless, at usual dose ranges, seizure rates are below 1% for all FGAs.

Tardive syndromes, including tardive dyskinesia
Tardive syndromes are persistent abnormal involuntary movement disorders caused by sustained exposure to antipsychotic medication, the most common of which are tardive dyskinesia, tardive dystonia, and tardive akathisia.

They begin later in treatment than acute dystonia, akathisia, or medication-induced parkinsonism and they persist and may even increase, despite reduction in dose or discontinuation of the antipsychotic medication. Typically, tardive dyskinesia presents as "involuntary athetoid or choreiform movements (lasting at least a few weeks) generally of the tongue, lower face and jaw, and extremities (but sometimes involving the pharyngeal, diaphragmatic, or trunk muscles)", whereas tardive dystonia and tardive akathisia resemble their acute counterparts in phenomenology. Tardive dyskinesia has been reported after exposure to any of the available antipsychotic medications.

Tardive dyskinesia occurs at a rate of approximately 4%-8% per year in adult patients treated with FGAs, a risk that appears to be at least three times that observed with SGAs. Various factors are associated with greater vulnerability to tardive dyskinesia, including age greater than 55 years; women; race/ethnicity; presence of a mood disorder, intellectual disability, or central nervous system injury; and past or current akathisia, clinically significant parkinsonism, or acute dystonic reactions.

Although the majority of patients who develop tardive dyskinesia have mild symptoms, a small proportion will develop symptoms of moderate or severe degree. Tardive dyskinesia can have significant effects on quality of life and can be associated with social withdrawal. Although the impact appears to be influenced by the severity, individuals with mild symptoms can also experience negative effects on quality of life.

Evaluation of the risk of tardive dyskinesia is complicated by the fact that dyskinetic movements may be observed with a reduction in antipsychotic medication dose, which is termed a withdrawal-emergent dyskinesia.

Fluctuations in symptoms are also common and may be influenced by factors such as psychosocial stressors. Furthermore, spontaneous dyskinesias, which are clinically indistinguishable from tardive dyskinesia, have been described in elderly patients, before the advent of antipsychotic medications and in up to 20% of never-medicated patients with chronic schizophrenia.

OPHTHALMOLOGICAL EFFECTS

The most common ophthalmological effects of antipsychotic medications are related to the anticholinergic effects of these agents and include blurred vision and exacerbation of open-angle glaucoma.

With SGAs, evidence does not suggest any increase in the likelihood of cataract development.

Although adverse ophthalmological effects of antipsychotic medications are infrequent, encouraging regular eye care is important to maintaining good vision for individuals with schizophrenia, particularly due to high rates of diabetes and other health conditions that can affect sight.

OTHER SIDE EFFECTS

Anticholinergic effects

The anticholinergic effects of some antipsychotic medications (along with the anticholinergic effects of antiparkinsonian medications, if concurrently administered) can produce a variety of peripheral side effects, including dry mouth, blurred vision, constipation, tachycardia, urinary retention, and effects on thermoregulation (e.g., hyperthermia in hot weather). Central anticholinergic effects can include impaired learning and memory and slowed cognition.

Because most anticholinergic side effects are mild and tolerable, they are often overlooked. Nevertheless, they can have multiple implications for patients, including impaired quality of life and significant health complications.

For example, dry mouth is associated with an increased risk for multiple dental complications and drinking high-calorie fluids in response to dry mouth can contribute to weight gain. The muscarinic receptor antagonist properties of antipsychotic drugs can be particularly problematic in older individuals and can contribute to problems such as urinary retention, confusion, fecal impaction, and anticholinergic toxicity (with delirium, somnolence, and hallucinations). Anticholinergic properties of antipsychotic or antiparkinsonian medications can also precipitate acute angle-closure glaucoma, although patients with treated glaucoma seem to be able to tolerate these medications with careful monitoring.

The propensity of an antipsychotic medication to cause anticholinergic effects should be considered when choosing an antipsychotic agent initially, particularly in older individuals or those with physical conditions that may confer a greater risk of anticholinergic complications. In selecting a medication, it is also important to keep in mind the total anticholinergic burden from antipsychotic medications, antiparkinsonian medications, urologic medications (e.g., oxybutynin), non-selective

antihistamines (e.g., hydroxyzine, diphenhydramine), and other medications with anticholinergic side effects. For this reason, antiparkinsonian medications with anticholinergic properties are not typically administered on a prophylactic basis. When anticholinergic side effects do occur, they are often dose-related and thus may improve with lowering of the dose or administering the medications that have anticholinergic properties in divided doses.

Fever

Fever (>38°C) should prompt assessment for possible etiologies including NMS or infection.

In hot weather, the possibility of heat stroke should be considered in patients who do not have access to air-conditioned environments due to the increased risk of heat-related events in individuals with psychiatric illness and the effects of some antipsychotics and anticholinergic agents on thermoregulation.

Sedation

Sedation is a very common side effect of antipsychotic medications. This effect may be related to antagonist effects of those drugs on histamine, adrenergic, and dopamine receptors. Sedation is most pronounced in the initial phases of treatment, as many patients develop some tolerance to the sedating effects with continued administration.

For agitated patients, the sedating effects of these medications in the initial phase of treatment can have therapeutic benefits. Bedtime sedation can also be desirable for patients who are having difficulty sleeping. However, persistent sedation, including daytime drowsiness, increased sleep time, and reduced cognitive acuity, can interfere with social, recreational, and vocational function.

Lowering of the daily dose, consolidation of divided doses into one evening dose, or changing to a less sedating antipsychotic medication may be effective in reducing the severity of sedation. Coffee or other caffeine can be helpful in the morning, but can also interact with medications (e.g., contribute to tachycardia, raise blood levels of medications including clozapine). Adding a stimulant medication is not typically helpful and can lead to additional side effects. If sedation or the risk of sedation is significant (e.g., during initial clozapine titration), patients should be cautioned not to drive or engage in potentially hazardous activities.

Sialorrhea

Sialorrhea (or hypersalivation) is a frequent side effect of clozapine but can also be observed with other antipsychotic medications. The etiology of sialorrhea is unclear but may relate to decreased saliva clearance, although actions on muscarinic or α-adrenergic receptors have also been postulated.

Sialorrhea can contribute to reductions in quality of life and can also be associated with complications such as aspiration pneumonia.

During the day, patients can be encouraged to chew sugarless gum, which stimulates the swallowing reflex. Because sialorrhea may be more bothersome at night, patients may be advised to place a towel on their pillow and change to a clean towel in the middle of the night to minimize discomfort.

Pharmacological approaches to address sialorrhea include use of low dose or topical anticholinergic medications, such as glycopyrrolate or sublingual ophthalmic atropine 1% drops.

Weight Gain

Weight gain occurs with most antipsychotic agents and appears to relate to actions of these medications as histamine H1 receptor antagonists, although actions on serotonin and muscarinic receptors may also play a role.

There is substantial variability in the amount of weight gain that will occur in an individual patient who is treated with a specific antipsychotic medication. Typically, weight gain is progressive over the first six months of treatment, although some patients continue to gain weight indefinitely. In addition, younger individuals who are experiencing a first episode of psychosis may be more likely to gain weight with antipsychotic medication than older individuals. In identifying individuals with schizophrenia who experience weight gain with antipsychotic treatment, self-reported awareness may be less effective than objective measurement.

Obesity, in general, can contribute to an increase in risk for mortality and morbidity including increased rates of cardiovascular disease, hypertension, cancers, diabetes, osteoarthritis, and sleep apnea. Consequently, weight gain with antipsychotic medications is also likely to contribute to an increase in physical health conditions and mortality. Prevention of weight gain should, thus, be a high priority. Efforts should be made to intervene proactively with weight gain of 5 to 10 pounds, as people who are obese rarely lose more than 10% of body weight with weight loss regimens.

Nutritional approaches may be suggested for their benefits for overall health as well as for weight. Such approaches include specialized mental health interventions, in-person community interventions (e.g., Weight Watchers), services that include meal delivery, or internet-based interventions. In addition, some programs have begun to integrate dieticians into the treatment team, given the nutritional challenges that exist for many individuals with serious mental illness.

Of the pharmacological treatments that have been assessed, metformin has been shown to be safe in individuals without hyperglycemia, shows modest benefits on weight (with average weight loss of 3-4 kg), and can reverse metabolic abnormalities in patients with obesity or other metabolic problems.

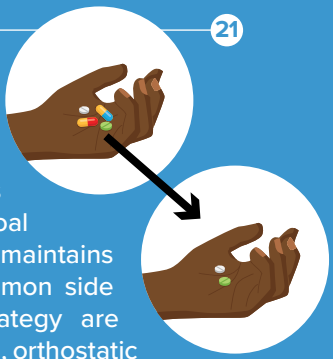
Another consideration for a patient who has experienced significant weight gain with antipsychotic treatment is to change or augment treatment with a medication with lower weight-gain liability.

When possible, other medications that can cause weight gain (e.g., valproate) should be tapered and discontinued. Such decisions need to consider the extent of the patient's response to the current medication regimen, the risks to the patient if relapse occurs with a medication change, and the likelihood that a medication change will be beneficial in terms of weight loss or other side effects. In any patient with weight gain, it is also important to assess for other contributors to metabolic syndrome.

The benefits of exercise appear to be small in terms of weight loss in individuals with schizophrenia. Nevertheless, many individuals with schizophrenia do not engage in physical activity and exercise can be suggested for its benefits to overall health, improved cardiorespiratory fitness and other aspects of functioning.

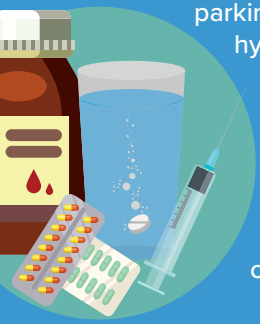
Side Effect Management

The previous section detailed the adverse events that may be encountered with antipsychotic medications. The following four strategies will help you manage these side effects so that the patient can still receive the most benefit from your chosen treatment, whilst minimising the impact on their day-to-day life.



STRATEGY 1: LOWER THE DOSE

This strategy is best when the adverse effect is dose-related and not medically urgent. The goal is to get the patient on the lowest dose that maintains efficacy while minimizing side effects. Common side effects successfully managed by this strategy are parkinsonism, sedation, hyperprolactinemia, orthostatic hypotension and anticholinergic effects.



STRATEGY 2: SWITCH THE PATIENT TO AN ANTIPSYCHOTIC WITH A DIFFERENT ADVERSE EFFECT PROFILE

More information about side effect profiles can be found in the second booklet of this series called Treatment options in Schizophrenia.

Switching to a medication that is less likely to cause the problem has proven effective in addressing dyslipidemias or weight gain. Switching antipsychotics is ideally done gradually using a cross-titration completed within two to four weeks.

STRATEGY 3: USE A NONPHARMACOLOGICAL INTERVENTION

This strategy has been moderately useful in addressing weight gain and related dyslipidemias through diet and exercise programs.

STRATEGY 4: TREAT THE SIDE EFFECT WITH A CONCOMITANT MEDICATION

This is a common, yet suboptimal, approach because beneficial effects of concomitant medications are often modest, and these medications may have side effects of their own, or introduce the potential for drug-drug interactions with existing therapies.

Non-Response or Partial Response to Treatment

If the patient shows no significant improvement after several weeks of treatment, or if improvement plateaus, it is important to consider what factors might be influencing treatment response.

Such factors include:

- non-adherence
- concomitant substance use
- rapid medication metabolism
- poor medication absorption
- interactions with other medications and
- other causes of altered drug metabolism, such as smoking

If no factors have been identified that would affect treatment response, raising the dose for a finite period can be tried. If this fails, a different antipsychotic medication should be considered.

For all patients with treatment-resistant schizophrenia, it is important to conduct a review of the treatment plan at periodic intervals.

In addition to a review of prior medication trials, it is essential to review the psychosocial treatments that a patient has received and whether addition of one or more psychosocial interventions would be of benefit.

Addressing Non-Adherence

Maintaining adherence to treatment is often challenging, and poor adherence is associated with poor outcomes, including increased risks of relapse, hospitalization, and suicidal and aggressive behaviours.

By successfully identifying the causes of non-adherence, you will be better equipped to find strategies to combat it. A list of common issues that influence adherence can be found in the booklet of the same title: preparing people with schizophrenia for a better future.

Lack of awareness of illness

Forgetting to take doses

Difficulties managing complex regimens

Aversion to a particular format such as injections

Conditions like depression or substance abuse

Cultural beliefs about illness and treatment

Other Concomitant Psychiatric & Health Conditions

Depressive symptoms are common in individuals with schizophrenia. Likewise, many individuals with schizophrenia may have experienced adversity or childhood violence. The impact of these experiences will need to be considered as part of a patient-centred treatment plan.

Co-occurring anxiety disorders may also be present.

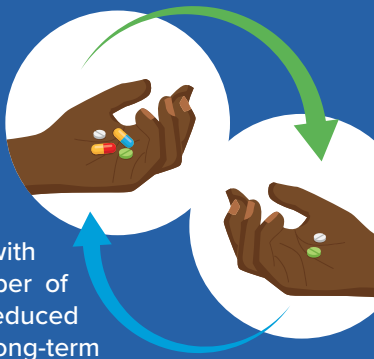
Any treatment plan must take into account medications being taken for concomitant psychiatric symptoms, as it is possible – as in the case of benzodiazepines or stimulants – that these medications might affect outcomes.

Concomitant health conditions are more frequent in individuals with serious mental illness in general and schizophrenia in particular. Such disorders or other health conditions include but are not limited to:

- poor oral health
- hepatitis C infection
- HIV infection
- Cancer
- Obesity
- Diabetes

These disorders, if present, can contribute to increased mortality or reduced quality of life and some may be induced or exacerbated by psychiatric medications' side effects. It is therefore important that patients have access to primary care clinicians who can work with the psychiatrist to diagnose and treat concurrent physical health conditions. The psychiatrist may also provide ongoing monitoring and treatment of common medical conditions in conjunction with primary care clinicians.

Continuing & Switching Medications



As there is no cure for schizophrenia, the aim of the treatment is to control the symptoms through ongoing treatment.

For patients whose symptoms have improved with an antipsychotic medication, there are a number of benefits to maintenance treatment, including reduced risks of relapse. But it should be noted that long-term use of antipsychotic medications could be associated with a greater incidence of side effects such as weight gain, sedation, and movement disorders.

However, these risks may be able to be mitigated by preventive interventions and careful monitoring for side effects. Nevertheless, as treatment proceeds the pluses and minuses of continuing on an antipsychotic medication should be reviewed with the patient and – where possible – family members, caregivers or other persons of support.

For most patients, it will be optimal to continue with the same medication. Nevertheless, under some circumstances, it may be necessary to change from one antipsychotic medication to another.

For example, a patient may have experienced some degree of response to initial treatment but may still have significant symptoms or difficulties in functioning that would warrant a trial of a different medication.

Other reasons might be the emergence of side effects such as weight gain or diabetes, medication availability, or changes in the suitability of oral versus injection formats.

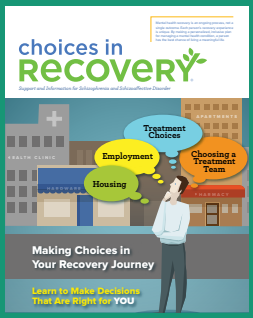
Conclusion

Schizophrenia is a distressing condition. However, with timely diagnosis, careful treatment planning, the use of first-generation and second-generation antipsychotic medications and appropriate psychosocial interventions, we are able to effectively treat the symptoms of schizophrenia and help patients live fulfilling lives.

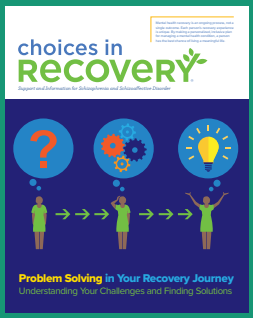
Remember, one of the best interventions you can make as a healthcare professional is to encourage and promote proactive collaboration between yourself, the patient, and his or her caregiving team.

Further Information

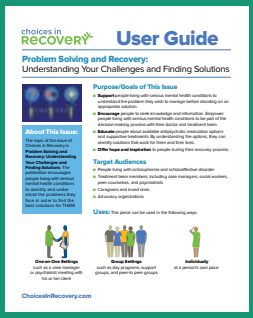
You may find the following booklets useful in providing further information about the topics covered in this booklet:



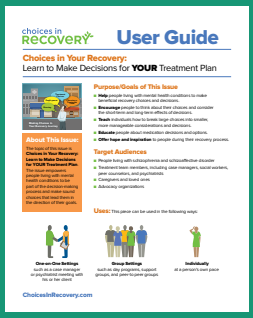
Helps your patients make choices and decisions along their mental health recovery journey



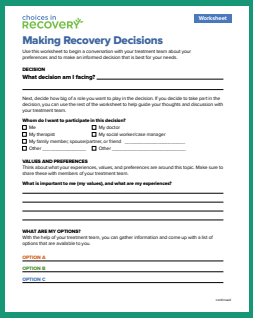
Helps patients find the right treatment options



Encourages patients to identify and understand the problems they face in order to find the best solutions for them



Explains how the "Making Choices" newsletter may help patients make positive choices and decisions



Helps to guide conversations between a patient and their treatment team to help them make informed decisions

These can be found on: *www.choicesinrecovery.com/treatment-team-center/resources-for-recovery-toolkit.html*

Reference

Keepers GA, et al. The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia. Am J Psychiatry 2020 Sep 1; 177(9):868-872. doi: 10.1176/appi.ajp.2020.177901.

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